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The Histological Structure of the Albino Rat Thyroid and Pituitary Glands After the Administration of 2-Thiouracil and 6-n-Propyl Thiouracil

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THE HISTOLOGICAL STRUCTURE OF THE ALBINO RAT THYROID AND PITUITARY GLANDS AFTER THE ADMINISTRATION OF 2-THIOURACIL AND 6-n-PROPYL THIOURACIL

by

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LIFE

Gareth Benway Gish was born in Saint Louis, Missouri, September 2, 1921.

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THE HISTOLOGICAL STRUCTURE OF THE ALBINO RAT THYROID AND PITUITARY GLANDS AFTER THE ADMINISTRATION OF 2-THIOURACIL AND 6-n-PROPYL THIOURACIL

Approximately eight years ago the first thiourea compound was found to have an influence upon the thyroid gland. The writer desired to determine the histological effect of feeding 2-thiouracil and 6-n-propyl thiouracil upon the parenchyma of the thyroid and pituitary gland. The drugs were given to white albino rats of the Sprague-Dawley strain.

The effects of feeding 2-thiouracil have been studied to a greater degree than the administration of 6-n-propyl thiouracil.

To the knowledge of the writer, no one has made a comparative study of the effects of the above mentioned drugs on the thyroid and pituitary structure.

HISTORY

The first results of thiourea compounds were reported by Kennedy (11) in 1942. He observed that goitrogenic substances in rape seed suggested a derivative of thio-urea. He fed allyl thio-urea to rats and observed hypertrophy and hyperplasia of the thyroid gland and an accompanying loss of colloid from the thyroid follicles. The changes were similar, in the thyroid and pituitary, to those produced by a diet containing rape seed.

In 1943 Astwood, Sullivan, Bissell and Tyslowitz (3) determined the actions of certain sulfonamides and thiourea upon the thyroid gland of rats of the Long-Evans strain. These substances caused an enlarged, hyperplastic, hyperemic thyroid coincident with a decreased food intake, decreased growth and development. The hyperplasia was not altered by the feeding of iodine, but was eliminated by the administration of thyroid powder. The authors attribute the hyperplasia to the failure of thyroid hormone synthesis by the thyroid gland.

Astwood (2) 1943, studied the effects of 106 compounds for their ability to inhibit the thyroid gland. Their efficiency was based upon their ability to bring about thyroid hyperplasia.

2-thiouracil was found to be the most effective derivative of thiourea. He found that thiocyanates were effective only in the absence of supplemental iodine. The feeding of iodine to thiourea treated animals had no effect upon the thyroid gland.

MacKenzie and MacKenzie (14) in 1943, observed that there was a reduction of colloid and an increase in the height of the follicular epithelium. The pituitary gland showed evidence of thyroidectomy cells. Thiourea was found to be eight times more effective than any of the sulfonamides. They also found that hypophysectomy prevented this hyperplasia as did the feeding of thyroxin. The first hypothesis that the enlargment of the thyroid was mediated through the anterior lobe of the hypophysis is made but other causative factors could not be dismissed at this time.

Thiouracil was found to have a retarding effect upon the Wistar strain of rats which was apparent within ten days following treatment. This impairment of growth involved the entire body, except the thyroid, and could not be abolished by the administration of the growth hormone. An examination of essentially all of the body tissues showed no alterations due to thiouracil except those noted in the thyroid gland as reported by Williams, Weinglass, Bissell and Peters (22) in 1944. These workers report that they could not observe any changes in the cellular structure of the anterior lobe of the hypophysis which is contrary to the report of the MacKenzies (14) 1943.

There is further evidence of retardation of body growth furnished by Hughes (10) in 1944. His results were more dramatic than those cited previously, Williams, Weinglass, Bissell and Peters (22), 1944, but he used animals from the time of birth. These effects were similar to those seen in cretinism. These effects were due to thiouracil since if thyroxin was given concurrently or if the injections of thiouracil were not given daily these changes were prevented.

In 1944 Mixner, Reineke and Turner (17) reported that thiouracil and thiourea have the same effects in the White Plymouth Rock chick when fed daily to two-day-old chicks for 14 days. This is in contrast to the report of MacKenzie and MacKenzie in 1943 (14). The effects were greater in the female than in the male. Here again the feeding of thyroxin prevented the enlargment of the thyroid gland and the female chick required greater amounts of thyroxin to offset the effects of the thiouracil and thiourea. Nine breeds of chickens were tested and they all reacted favorably to these drugs.

Franklin, Lerner and Chaikoff, in 1944, (8) used radioactive iodine as an indicator of the ability of the thyroid gland to concentrate the iodine which was injected. From their work, they were able to report that the thyroid gland could not concentrate or convert the iodine into thyroxin and diiodotyrosine as well as the control animal. The treated glands were able to recover and function normally within two weeks after cessation of treatment.

At the same time, Astwood and Bissell, in 1944 (4) found that the administration of thiouracil caused a nearly complete disappearance of iodine from the thyroid gland within five days. These effects were inhibited by hypophysectomy or by thyroxin injections. Withdrawal of the drug caused the follicle to return to normal and the rapid accumulation of colloid but this colloid is nearly devoid of iodine. Large amounts of thyrotropic hormone caused a similar hyperplasia of the gland but without the accompanying loss of iodine. They state that these results support the view that thiouracil inhibits the formation of the thyroid hormone but give no indication of the mechanism responsible for these effects.

Baumann, Metzger and Marine, 1944, (5) found that thiourea caused thyroid hyperplasia in the rabbit, which other investigators had found for the rat, mouse, dog and chick. They found that large quantities of iodine were ineffectual in preventing a rapid hyperplasia. The loss of iodine from the gland was excreted in the urine. This inhibition of thyroxin formation indicates that thiourea has a thyrostatic action on the thyroid cells of the rabbit.

In 1944 Rawson, Tannheimer and Peacock (18) compared the effectiveness of potassium thiocyanate and thiouracil in preventing the uptake of radioactive iodine in rats of the Sherman strain. They found that both drugs have a goitrogenic effect but that thiouracil was more effective than potassium thiocyanate. Potassium thiocyanate actually increases the ability of the thyroid gland to take up the radioactive iodine whereas thiouracil almost prevents the uptake of any of the radioactive substance.

Many workers stated that the administration of thyroxin prevented the thiourea derivatives from having any effect and that these drugs have no effect on the thyroxin per se. But, Dietrich and Beutner 1944 (6) have found that thiouracil does interfere with orally administered thyroxin. They conclude that thiouracil and thiourea in addition to preventing the synthesis of the thyroid hormone also has some effect on the thyroxin fed to white mice.

To have an understanding of the similarities of producing hyperplasia in the thyroid gland by both thiouracil and thyrotropic hormone Larson, Keating, Peacock and Rawson 1945 (12) used radioactive iodine. They found that the hyperplasia produced by the two substances were similar and that, except for the lag in onset when thiouracil was used, the results were the same. The chicks were found to react as the rats used by Rawson, Tannheimer and Peacock, 1944 (18), and Franklin, Lerner and Chaikoff, 1944 (8). Upon withdrawal of thiouracil, the thyroids of the treated chicks rapidly acquired a capacity to collect radioactive iodine in much larger quantities than controls and in amounts similar to those thyroids made hyperplastic by thyrotropic hormone injections.

The same workers, Larson, Keating, Peacock and Rawson, 1945 (13) repeated their former work and in every instance found the results were the same in the chicks that were given the thyrotropic hormone and thiouracil; i. e., thiouracil inhibited the collection of radioactive iodine by the thyroid of the normal chick given thiouracil one hour before the iodine, by the thyroid made hyperplastic by the injections of thyrotropic hormone when given thiouracil one hour before the iodine and the thyroid made hyperplastic by the administration of thiouracil. The effect of thiouracil on the collection of radioactive iodine was largely dissipated within twenty-fours after an injection of 10 mgm. in the normal chick.

Reineke, Mixner and Turner, in 1945 (19), found that there was more thyroxin required to return the thyroid gland to normal weight than was needed to return the metabolic rate to normal. This supported the work of Dietrich and Beutner, 1944 (6) that thiourea had an effect of inactivation on thyroxin per se.

Thiourea and its derivatives have an effect of producing pulmonary edema and pleural effusion in old rats, Marine and Baumann (16) 1945. This intoxication by thiourea is influenced by old age as seen in the number of animals that died and the rapidity of death after the injection of thiourea.

Malkiel 1946 (15) in trying to explain the mode of action of thiourea and thiouracil restates the proposals of MacKenzie and MacKenzie 1943 (14); a) Retention of the thyroxin by the thyroid gland, b) Elevation of tissue requirements for thyroxin through the inhibition of some enzyme system, c) Destruction of the circulating hormone or its inactivation, d) Depression of the rate of thyroxin formation. Other recent publications, Larson, Keating, Peacock and Rawson, 1945 (12) (13); Reineke, Mixner and Turner, 1945 (19), support the postulation of Astwood, Bissell, Sullivan and Tyslowitz, 1943 (3) that the action is directly upon the thyroid gland so that there is interference with the production of the thyroid hormone. Inhibition of the secretion of the thyroid hormone permits an increase of the thyrotropic hormone secretion by the anterior hypophysis resulting in a compensatory hypertrophy and hyperplasia of the thyroid gland.

VanderLaan and Bissell, 1946 (21), relates that propyl thiouracil has been found to be the most potent anti-thyroidsubstance used in the treatment of hyperthyroidism in the human. In their experience with rats they show that thiocyanate interferes with the uptake of iodine unless there is an abundance of iodine in the diet. Thiouracil on the other hand does not seem to interfere with the uptake of the iodine by the thyroid but, by interfering with the synthesis of the thyroid hormone, this iodine is soon lost from the gland.

The rhesus monkey, as reported by Engle and Aranow in 1946 (7), showed a histological structure not reported as occurring in other animals. The thyroid gland of monkeys treated with 0.8 gm. thiouracil for 73 days showed an intra-follicular vesicle that was characteristic in these animals. This vesicle arose from the follicular epithelium and was attached by a single pedicle. The vesicles developed as an invagination of the follicular epithelium and the surface of the vesicle was completely delimited by an intact epithelial membrane. The hyperplastic thyroid returned to normal within 34 days after cessation of the thiouracil treatment, and by the 49th day the thyroid gland was completely normal in every respect.

Aranow, Engle and Sperry, 1946 (1), studied the effects of thiouracil on four adult female rhesus monkeys. There was no significant change in weight or other changes that were of importance for thiouracil research. They found, as in the human, that a neutropenic condition developed which could not be corrected by folic acid or pyridoxine therapy. The most important effect was noted in the appearance of irregular menstrual periods.

Grasso, 1946 (9), reports that after five months treatment the thyroid gland assumed a structure somewhat similar to the normal. Prior to this time the histological changes like congestion, reabsorption of the colloid, increased height of the epithelium, and hyperplasia were described. He reported that the thyroid cells were really more active but that the product secreted had a very low hormonal activity due to the lack of thyroxin in the secretion.

In 1945, Thomas (20) reported that the parenchyma of the thyroid was reduced and compressed by the presence of extremely large sinusoidal spaces filled with blood. The vessels were the predominant feature of the gland and the parenchyma was reoriented about them. Both the inter follicular and the intrinsic capillaries were affected in this change. The interfollicular capillary enlarged to the point where it became a giant capillary. The intrinsic capillary enlarged to the place where it projected between adjacent epithelial cells. These projections of the intrinsic capillaries became true intraepithelial capillaries

MATERIALS AND METHODS

Litter mate male and female rats of the Sprague-Dawley strain were used in this study. The thyroid and pituitary glands were used throughout for study.

The drugs, 2-Thiouracil and 6-n-propyl Thiouracil were given to the animals by three methods: by dissolving the drugs in the drinking water; mixing the drugs with the food; and by oral administration (intubation).

The ages of the animals varied from 28 to 196 days and the duration of the experiment varied from one month to a year.

The normal and experimental animals were maintained under the same conditions insofar as it was possible to control variants. Purina Fox Chow was fed to the animals without further supplementation of the diet.

While the experiment was in progress there were some deaths among the animals due to respiratory infections. The sick animals were separated from those that were not affected and did not receive any treatment. The animals that recovered were replaced with their cage mates and those animals that died were not used in any manner for purposes relating to this problem.

Procedure of Preparing the Drugs for Administration.

The drugs, when administered orally, were mixed in a two cubic centimeter syringe. In this manner, the amount of drug given could be carefully controlled.

When the drug was mixed with the Purina Fox Chow, the Chow was first thoroughly ground by a mechanical grinder. The drugs were then mixed on the basis of fifteen grams of food per animal per day. A careful weighing of the food was made daily to ascertain if the animals were eating the correct amount of food to maintain the required dosage level. The ground food and drugs were mixed in a rotary mixer to guarantee an even distribution of the drug throughout the food and an evenly ground food substance.

The drug administered by the route of the drinking water was carefully based on the amount of water consumed per cage of animals per day. In this manner, the animals were never given more than the required amount of drug in any twenty-four period.

Histological Methods.

There was only one procedure employed for the preparation of the thyroid and pituitary glands for study and this was followed throughout the experiment in the same manner.

A. Fixation by the Zenker-Formol Technique.

1. The thyroid and pituitary tissues were removed from the animals and placed in the Zenker-Formol fixing solution for twenty-four hours.
2. The tissues were washed in distilled water for forty-eight to seventy-two hours or until the water remained free from any coloration of the fixing solution.
3. Dehydration of the tissue was accomplished by using varying percentages of alcohol (35%, 50%, 70%, 80%, 95% and 99% for one hour periods.
4. The excess mercuric chloride was removed by the use of iodine in the 70% alcohol. This process usually took thirty-six to forty-eight hours.
5. A mixture of absolute alcohol and xylol, fifty per cent of each, was placed over the tissue for one hour.
6. The tissues were cleared with pure xylol for one hour.
7. Next a mixture of xylol and paraffin, fifty per cent of each was placed over the tissues for one hour. The paraffin had a melting point of fifty-four to fifty-six degrees.
8. The tissues were infiltrated with pure paraffin, fifty-four to fifty-six degrees melting point, for forty-five minutes.
9. The tissues were imbedded in the same type paraffin.

10. The tissue containing paraffin blocks were stored at room temperature until ready for cutting. Serial sections of the thyroid and pituitary were cut at 6 to 7 micra.

B. Staining Procedures.

1. The sections of tissue were deparaffinized, hydrated and then stained by two methods.

   a. Mallory Technique.

      i. The tissue sections were stained in solution I for ten minutes. These sections were thyroid and pituitary gland specimens.

      ii. The sections were quickly rinsed in distilled water two times.

      iii. The thyroid sections were placed in solution II for fifteen minutes while the pituitary sections were stained for twenty-five minutes.

      iv. The tissue sections were placed in distilled water to remove the excess stain.

      v. The sections were placed in ninety-five per cent alcohol for a period of one minute. While the sections were in the alcohol, the sections were agitated to increase the removal of excess water.

      vi. The sections were placed in absolute alcohol until thoroughly dehydrated.

vii. To clear the sections, pure xylol was used.

viii. The sections were cover slipped with piccolyte.

b. Iron Hemotoxylin Technique (short method).

Constituents:

1% hemotoxylin in absolute alcohol..........25 cc.

1.2% ferric chloride in distilled water.....25 cc.

i. The thyroid sections were deparaffinized and hydrated and then stained in the above solution for fifteen minutes.

ii. If necessary the sections were destained in a solution of two parts water to one part two per cent solution of ferric chloride.

iii. The sections were washed in tap water and then placed in distilled water for ten minutes. The were run up through the same series of alcohol concentrations that were used in hydration.

iv. The sections were cleared in xylol and cover slipped with the use of piccolyte.

The use of the Mallory technique shows the active colloid of the thyroid gland as a light blue, while the older, stored colloid appears orange-yellow.

The iron hemotoxylin stain shows the colloid of the active thyroid follicle to be a grey-blue and the stored colloid appears very light grey.

Pituitary cellular construction is accentuated by the use of the Mallory stains. The eosinophiles appear orange-yellow with red nuclei, the basophiles are blue with light red nuclei, and the chromophobes are seen as a pale grey-blue, indistinct cell with the nuclei almost unobservable.

OBSERVATIONS

Histological study shows that the thyroid and pituitary glands of the treated animals undergo marked changes. Within a period of one month, these changes are readily apparent in the thyroid. The colloid is reduced in amount and has the appearance of active colloid. There is little to no in active colloid apparent in the follicles. There are many follicular cells that are normal but the cell height in many of the follicular units has increased and the follicles show an irregular, unorganized structure when compared to the normal.

The follicular cells have changed from the normal cuboid cell to a low columnar type of cell with the nuclei less pycnotic and no longer occupying the basal portion of the cell. The cell cytoplasm is beginning to show a granular, uneven appearance and the nuclei in many of the follicles are larger and not as dense in appearance as those in the follicles that are evidencing many of the changes. The nuclei in the changing cells show the presence of nucleoli and a clear nucleoplasm.

There is evidence of an increased blood supply to the thyroid glands of the experimental animals that is not evident in the control animals. This is seen by the increased space between the follicles and the increased diameter of the lumen of the capilliform sinusoids surrounding the follicles.

In contrast to these readily apparent changes in most of the follicles, there were some follicles that showed changes only by the increase in the cell height of the follicular epithelium. The nucleus of these cells appeared pycnotic but occupied a medial position in the cell. The outline of the above follicles was still regular in appearance and had not yet begun to show the irregularities seen in the follicles that had been radically affected.

The thyroid gland of the control rat shows an abundance of inactive colloid in well rounded follicles. The lumen of the surrounding vessels was quite small and the distance between the follicles was also small.

The pituitary of the experimental animal shows more prominent basophiles with an abundance of cytoplasm which stains a brilliant blue and has a granular appearance when stained by the Mallory technique. The normal animal has basophiles with the blue staining cytoplasm but, the cells are smaller and basophiles are not as bundant. The sinusoids of the experimental animals are larger than those observed in the controls and there is an excess of red blood cells filling the sinusoids.

The thyroids of the two month experimental groups show a much more pronounced change than was seen in the one month groups. The follicular structure has changed to an even greater degree. The cell height is greater than was apparent in the one month animals. Here, as in the one month group, the control thyroids were normal in every respect.

The animals fed thiouracil show a greater blood supply than those of the one month group, but those animals fed propyl thiouracil showed follicles packed more closely together due to hyperplasia. The venous plexus appeared considerably enlarged. The colloid of the thiouracil treated animals is stained a very light grey while that present in the propyl thiouracil treated animals, though grey, is characterized by occasional pools of bright blue colloid. The colloid of the control animals still remains orange to orange-yellow of stored colloid.

The pituitary structure shows a change from that seen in the one month animals. The number and size of the acidophiles has decreased. There was no apparent increase in the number of basophiles but the cytoplasm, which stained a bright blue, appears increased in amount.

The histology of the thyroid gland from the four-month experimental animals appeared similar to that of the two-month period. A primary change is in the appearance of the colloid present in the follicles of the experimental animals. There is still blue colloid present, as seen in the shorter experimental period; but now an almost colorless, granular deposit or residue is seen in the follicle. The height of the follicular cells has begun to decrease and many more follicles are present. These follicles are very small when compared to those present in the control animals. The nuclei are resuming a pycnotic condition and the nucleoli seen previously in the experimental animals have disappeared. The follicular structure is assuming a highly disorganized appearance. The Golgi apparatus is seen between the nucleus and the lumen of the follicle in osmic acid stained sections (after Ludford). The thyroid gland shows a condition of hyperemia which is greater that that seen previously in the examination of the sections.

The acidophiles are decreased in number in the pituitary gland and the gland contains predominantly chromophobes and basophiles. The number of basophiles has not increased but they still show the bright blue cytoplasm in abundance. The gland is highly hyperemic and the sinusoids are very large.

The six-month groups show that the thyroid gland has changed to a greater degree than observed in the four-month groups of animals. The follicle cells have decreased in height and the nuclei appear very small and pycnotic. The venous plexus is quite large and the veins and arteries of the gland are enlarged.

The lumen of the follicle no longer shows any resemblance to that seen in the control animal. The follicular lumen is very irregular in outline and in some cases is completely absent. When the lumen is present there is no colloid apparent in the majority of the follicles. The colloid, when present, is the active type and is very minute in amount and there are many vacuoles along the periphery of the colloid indicating resorption. Even these follicles show that the cellular structure has been affected. The cell height has been reduced and the nuclei are very irregular in shape and show signs of pycnosis. The nucleoli have disappeared and the nuclei instead of being spherical, as seen previously, have become triangular in shape.

The pituitary shows enlarged sinusoids indicative of an increased blood supply. The acidophiles are much decreased in size. The basophiles and chromophobes appear to be in the same proportion as seen in the four-month groups of experimental animals. There are indications that the basophiles are not as large as they were and the amount of cytoplasm appears to be decreased but still has the bright blue color.

There is visible evidence that the propyl thiouracil has a much greater effect than the thiouracil. This is seen in the greater disruption of the follicular structure of the thyroid gland and the decrease in the size of the follicular cells and an increased hyperemia. Until this time, the differences were not so apparent, but following six months administration of the drugs the changes are great enough to be easily seen.

Examination of the nine-month groups of animals would seem to indicate that the thyroid glands of the treated animals have been able to return to a condition approximating that of the controls. The only apparent change is in the number of follicles. Only a slight increase in height of the epithelium was apparent and active and inactive colloid was present in the lumen of the follicles. The only evidence directly indicative of any effect of the drugs is the hyperemia of the gland. These changes are based on a comparison with the control animal.

The pituitary of the experimental animal gives evidence of changes that are more indicative of the effects of the drugs. The gland shows extreme hyperemia with an easily observable preponderance of chromophobes and basophiles over the normal amount seen in the anterior hypophysis. The acidophiles are not as numerous as they are in the control animal and they appear smaller and less granular.

The primary histological evidence indicating the administration of thiouracil for one year is the abundance of small follicles which contain the active type of colloid. The active colloid was more abundant than that which was observed in the nine-month group of animals. More inactive colloid also was observed for this period. The indications of treatment is the large number of very small follicles and the accompanying increase in the blood supply.

The control animals show large amounts of inactive colloid with some active colloid present in very small amounts in large follicles. This is in direct contrast to the experimental animals which show small amounts of inactive colloid and relatively large amounts of active colloid in the small, numerous follicles.

The hypophysis of the control animals show few basophiles, numerous chromophobes and many acidophiles. In the experimental animal there are small acidophiles and they are less abundant than in the controls. Increased numbers of chromophobes and a large number of basophiles were usually seen.

DISCUSSIONS AND CONCLUSIONS

The modifications in the structure of the thyroid gland which have been described through the six-month groups are very similar to those described by other workers. The primary effect produced by the administration of thiouracil, according to most investigators, is the cessation of thyroxin formation. This can be determined by the appearance of the histological sections of the thyroid gland. Following the administration of thiouracil, it has been observed that there is a disappearance of the stored colloid from the follicle. It may be assumed that, due to the lack of continuous secretion and synthesis of the hormone, there is an attempt by the gland to supply the hormone through the liberation of the stored product. This condition will eventually cause the appearance of smaller follicles by a mechanical means.

The fact that a reciprocal relationship exists between the thyroid and the pituitary gland has been previously established. When thyroxin is present in normal amounts, this hormone controls the elaboration of the thyrotropic principle by the beta cells of the anterior lobe of the hypophysis. Previous work has also demonstrated that a minimum secretion of thyroxin results in a stimulus to the beta cells of the anterior lobe of the anterior hypophysis. Experiments have further proven that the reverse condition may be produced. In this experiment the elaboration of thyroxin during the first month was sub-minimal, which may be assumed because:

1. The beta cells of the anterior lobe of the hypophysis become enlarged and the granulation is pronounced.
2. The beta cells may increase in number.
3. The cellular changes described above may cause the increased secretion of the thyrotropic principle.
4. The increased secretion of the thyrotropic principle causes the hyperplasia of the thyroid follicular epithelium.
5. The inactive colloid is withdrawn from the follicle by reabsorption.

During the two-and-four-month experimental periods the modifications which have been described for the first-month were more apparent. In other words, the thyroxin was minimal which resulted in the appearance of more prominent enlarged basophiles in the anterior hypophysis. The thyrotropic hormone was being elaborated in greater than normal amounts which caused the follicular epithelium to become columnar in appearance. The lumen of the thyroid follicles gradually disappeared due to the hyperplasia and the almost complete inhibition by the thiouracils. It was after the fourth month that small amounts of active colloid were still apparent in some follicles. However, during this period a colorless deposit also began to appear in the follicle.

The histological modifications of the thyroid during the sixth month may be considered as a continuation of the physiological process which has been outlined. The disappearance of the colloid from the follicles indicates a complete suppression of secretory activity of the thyroid epithelium. The epithelium of the follicle has become flattened, which may be considered a result of cellular exhaustion. The absence of the colloid and the flattening of the follicular epithelium causes the collapse of the follicle. The hypophysis shows a structure which is indicative of a continued hypersecretion of the thyrotropic hormone.

Some time between the six-month and nine-month experimental periods the 2-thiouracil and 6-n-propyl thiouracil have lost their effectiveness on the thyroid gland. This may be due to the development of a refractory state by the thyroid. It became apparent that 2-thiouracil and 6-n-propyl thiouracil had lost their effectiveness because:

1. The thyroid structure begins to resume its normal appearance.
2. The follicular epithelium increases in height showing

the return of the response to the thyrotropic hormone.

3. The follicles once more contain active colloid in very small but numerous follicles. Inactive colloid is seen in minute amounts.

At twelve months the experimental animals show more evidence of returning to normal for the following reasons:

1. The structure of the anterior lobe of the hypophysis has almost returned to that resembling the control animal.
2. The basophiles are more numerous than those in the control animal but they are not so prominent as they were previously.
3. The thyroid structure resembles that of the control animal in almost every respect.
4. The differences are in the larger amount of stored colloid now seen in the experimental animal and the hyperemia is no longer a prominent feature of the thyroid gland. There is still a slight hyperplasia.

SUMMARY

The administration of thiouracil and propyl thiouracil to normal albino rats resulted in enlarged, hyperemic, and hyperplastic thyroid glands. The modifications which occur in the thyroid gland were apparent within one month and became progressively greater through the sixth month. In the study of the nine-month experimental rats it was observed that the thyroid gland regresses from these conditions and approaches the condition of the normal thyroid. This regression is accentuated in the twelve-month group and the only histological evidence of the effects of the drugs are:

1. The small, numerous thyroid follicles contain varying amounts of the active type of colloid.
2. A thyroid follicular epithelium which is higher than that seen in the control.
3. Hyperemia, thought evident, has decreased from that seen in the thyroid glands removed from animals of the shorter experimental periods.

These drugs cause a change in the anterior pituitary which continues through the nine-month groups. These changes are:

1. The cytoplasm of the beta cells becomes increased in amount.
2. The number of beta cells may increase.
3. The acidophiles decrease in number and lose their granular appearance to a great degree.

The pituitary glands from the twelve-month experimental animals show:

1. A structure that is almost normal.
2. The basophiles are not so numerous as they were previously.
3. The ratio of acidophiles has increased and they appear to have resumed a more normal appearance.

From the results of this experiment one may conclude that the thiouracils have an inhibiting effect upon the secretion of the thyroxin which has a reciprocal action of causing an increase of thyrotropin to be secreted from the anterior lobe of the hypophysis.

The effects of the drugs are diminished in the nine-and-twelve-month experimental animals and the thyroid and pituitary glands return to a condition that is approximately normal.

The thyroid cells appear to become exhausted during the sixth month following the administration of the thiouracils but again respond to the stimulus of the thyrotropic hormone as seen in the nine-month and twelve-month animals. This ability to resume a near normal function may indicate a refractory state of the thyroid gland to the continued administration of 2-thiouracil and 6-n-propyl thiouracil.

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APPENDIX A

Animal Groups and Number in Group	Ave. Wgt. in Grams at Start of Expt.	Ave. Wgt. in Grams at Autopsy	Length of Expt.	Ave. Size of Thyroid at Autopsy
Thiouracil .025 gm. in water 2 rats	98	167	1 mo.	7.5 x 4.4 mm.
	(101)	(175)		8.0 x 4.9 mm.
	(89)	(159)		7.0 x 3.8 mm.
Thiouracil .025 gm. by tube 4 rats	93	171	1 mo.	6.0 x 3.8 mm.
	(93)	(166)		5.0 x 5.0 mm.
	(87)	(160)		6.0 x 4.1 mm.
	(95)	(175)		7.0 x 4.1 mm.
	(99)	(182)		7.0 x 3.0 mm.
Thiouracil .05 gm. in water 2 rats	87	140	1 mo.	6.5 x 4.0 mm.
	(85)	(139)		7.0 x 4.5 mm.
	(88)	(142)		6.0 x 3.5 mm.
Thiouracil .05 gm. by tube 4 rats	64	164	1 mo.	5.5 x 4.6 mm.
	(63)	(184)		6.0 x 4.5 mm.
	(64)	(162)		6.0 x 4.7 mm.
	(60)	(143)		5.0 x 4.5 mm.
	(68)	(166)		5.0 x 4.4 mm.
Average	85	160		6.4 x 4.2 mm.
Control	88	187	1mo.	5.0 x 3.0 mm.
	(112)	(291)		4.0 x 3.5 mm.
	(98)	(196)		7.0 x 5.0 mm.
	(70)	(194)		4.0 x 3.5 mm.
	(70)	(182)		5.0 x 3.0 mm.
	(66)	(129)		5.0 x 3.0 mm.
	(88)	(167)		7.0 x 5.0 mm.
	(83)	(157)		5.0 x 3.0 mm.
	(93)	(166)		5.0 x 3.0 mm.
	(96)	(178)		5.0 x 3.0 mm.

APPENDIX B

Animal Groups and Number in Group	Ave. Wgt. in Grams at Start of Expt.	Ave. Wgt. in Grams at Autopsy	Length of Expt.	Ave. Size of Thyroid at Autopsy
Thiouracil .025 gm. by tube 2 rats	171.5	188	2 mos.	6.5 x 2.5 mm.
	(173)	(184)		6.0 x 2.0 mm.
	(170)	(192)		7.0 x 3.0 mm.
Propyl Thiouracil .025 gm. by tube 3 rats	185	190	2 mos.	8.0 x 4.0 mm.
	(190)	(186)		8.0 x 4.0 mm.
	(185)	(196)		8.0 x 4.0 mm.
	(180)	(188)		8.0 x 4.0 mm.
Thiouracil .025 gm. in food 2 rats	200	184.5	2 mos.	8.0 x 4.0 mm.
	(200)	(185)		7.0 x 4.0 mm.
	(200)	(184)		9.0 x 4.0 mm.
Propyl Thiouracil .025 gm. in food 2 rats	208	193	2 mos.	8.0 x 4.0 mm.
	(212)	(192)		8.0 x 4.5 mm.
	(204)	(194)		8.0 x 3.5 mm.
Thiouracil .05 gm. by tube 2 rats	153	172	2 mos.	6.4 x 2.7 mm.
	(155)	(174)		6.6 x 3.0 mm.
	(151)	(170)		6.2 x 2.5 mm.
Propyl Thiouracil .05 gm. by tube 2 rats	165.5	190	2 mos.	8.0 x 3.0 mm.
	(170)	(192)		7.0 x 3.0 mm.
	(161)	(188)		9.0 x 3.0 mm.
Thiouracil .05 gm. in food 2 rats	167	164	2 mos.	7.5 x 3.0 mm.
	(177)	(178)		8.0 x 3.0 mm.
	(157)	(150)		7.0 x 3.0 mm.
Propyl thiouracil .05 gm. in food 1 rat	174	150	2 mos.	6.0 x 3.0 mm.
	(174)	(150)		6.0 x 3.0 mm.
Average	178	179	2 mos.	7.3 x 3.3 mm.
Control	175	182	2 mos.	5.0 x 2.3 mm.
	(173)	(194)		4.0 x 1.5 mm.
	(150)	(176)		5.0 x 2.0 mm.
	(186)	(186)		5.0 x 1.5 mm.
	(186)	(192)		5.0 x 2.0 mm.
	(168)	(176)		5.0 x 2.0 mm.
	(157)	(172)		5.0 x 2.0 mm.
	(195)	(178)		5.0 x 1.5 mm.

APPENDIX C

Animal Groups and Number in Group	Ave. Wgt. in Grams at Start of Expt.	Ave. Wgt. in Grams At Autopsy	Length of Expt.	Ave. Size of Thyroid at Autopsy
Thiouracil .025 gm. by tube 3 rats	167	227	4 mos.	8.6 x 4.8 mm.
	(194)	(272)		9.0 x 5.0 mm.
	(160)	(206)		8.0 x 5.0 mm.
	(147)	(204)		9.0 x 4.0 mm.
Propyl Thiouracil .025 gm. by tube 3 rats	171	229	4 mos.	8.3 x 4.0 mm.
	(216)	(290)		8.0 x 4.0 mm.
	(154)	(202)		8.0 x 4.0 mm.
	(152)	(195)		9.0 x 4.0 mm.
Thiouracil .025 gm. in food 2 rats	265	239	4 mos.	9.0 x 4.0 mm.
	(322)	(282)		9.0 x 4.0 mm.
	(209)	(196)		9.0 x 4.0 mm.
Propyl Thiouracil .025 gm. in food 1 rat	338	276	4 mos.	8.5 x 4.5 mm.
	(338)	(276)		8.5 x 4.5 mm.
Thiouracil .05 gm. by tube 2 rats	37.5	178	4 mos.	5.5 x 2.5 mm.
	(41)	(208)		6.0 x 3.0 mm.
	(34)	(148)		5.0 x 2.0 mm.
Propyl Thiouracil .05 gm. by tube 1 rat	(42)	(188)	4 mos.	8.0 x 4.0 mm.
	(42)	(188)		8.0 x 4.0 mm.
Thiouracil .05 gm. in food 2 rats	158	151	4 mos.	8.0 x 4.0 mm.
	(161)	(158)		8.0 x 4.0 mm.
	(155)	(144)		8.0 x 4.0 mm.
Propyl Thiouracil .05 gm. by tube 2 rats	154	141	4 mos.	8.0 x 4.0 mm.
	(156)	(148)		9.0 x 5.0 mm.
	(152)	(134)		7.0 x 3.0 mm.
Average	167	204	4 mos.	7.6 x 3.9 mm.
Control 8 rats	148	195	4 mos.	4.4 x 2.2 mm.
	(155)	(224)		4.0 x 3.0 mm.
	(154)	(240)		4.0 x 3.0 mm.
	(146)	(224)		4.0 x 2.0 mm.
	(331)	(228)		5.0 x 3.0 mm.
	(38)	(152)		4.0 x 2.0 mm.
	(38)	(182)		5.0 x 2.0 mm.
	(164)	(139)		5.0 x 2.0 mm.
	(160)	(172)		4.0 x 2.0 mm.

APPENDIX D (i)

Animal Groups and Number in Group	Ave. Wgt. in Grams at Start of Expt.	Ave. Wgt. in Grams At Autopsy	Length of Expt.	Ave. Size of Thyroid at Autopsy
Thiouracil .025 gm. by tube 3 rats	82	151	6 mos.	6.6 x 2.0 mm.
	(84)	(174)		6.0 x 2.0 mm.
	(73)	(130)		6.0 x 2.0 mm.
	(90)	(150)		7.0 x 2.0 mm.
Propyl Thiouracil .025 gm. by tube 2 rats	77	149	6 mos.	6.0 x 2.0 mm.
	(79)	(140)		5.0 x 2.0 mm.
	(75)	(159)		7.0 x 2.0 mm.
Thiouracil .025 gm. in food 3 rats	72	144	6 mos.	7.3 x 3.2 mm.
	(76)	(159)		8.0 x 3.0 mm.
	(69)	(134)		7.0 x 3.5 mm.
	(72)	(138)		7.0 x 3.0 mm.
Propyl Thiouracil .025 gm. in food 2 rats	74	124	6 mos.	6.5 x 4.0 mm.
	(77)	(144)		7.0 x 4.0 mm.
	(72)	(104)		6.0 x 4.0 mm.
Average	76	142	6 mos.	6.6 x 3.0 mm.
Control 5 rats	76	161	6 mos.	4.8 x 1.8 mm.
	(90)	(186)		6.0 x 1.5 mm.
	(83)	(150)		5.0 x 2.0 mm.
	(70)	(148)		4.0 x 2.0 mm.
	(69)	(154)		4.0 x 2.0 mm.
	(69)	(166)		5.0 x 1.5 mm.

APPENDIX D (ii)

Animal Groups and Number in Group	Ave. Wgt. in Grams at Start of Expt.	Ave. Wgt. in Grams at Autopsy	Length of Expt.	Ave. Size of Thyroid at Autopsy
Thiouracil .05 gm. by tube 3 rats	98	171	6 mos.	6.6 x 3.0 mm.
	(95)	(186)		7.0 x 3.0 mm.
	(104)	(170)		6.0 x 3.0 mm.
	(95)	(156)		7.0 x 3.0 mm.
Propyl Thiouracil .05 gm. by tube 2 rats	107	144	6 mos.	7.5 x 3.5 mm.
	(103)	(144)		8.0 x 3.0 mm.
	(111)	(143)		7.0 x 4.0 mm.
Thiouracil .05 gm. in food 2 rats	41	112	6 mos.	6.5 x 3.2 mm.
	(46)	(116)		6.0 x 3.0 mm.
	(36)	(109)		7.0 x 3.5 mm.
Propyl Thiouracil .05 gm. in food 3 rats	53	145	6 mos.	6.3 x 4.2 mm.
	(53)	(160)		6.0 x 5.0 mm.
	(52)	(141)		6.0 x 4.0 mm.
	(53)	(135)		7.0 x 4.0 mm.
Average	75	143	6 mos.	6.8 x 3.5 mm.
Control 5 rats	85	191	6 mos.	5.6 x 2.0 mm.
	(134)	(300)		5.0 x 2.0 mm.
	(111)	(190)		5.0 x 2.0 mm.
	(110)	(181)		6.0 x 2.0 mm.
	(25)	(126)		6.0 x 2.0 mm.
	(47)	(160)		6.0 x 2.0 mm.

APPENDIX E

Animal Groups and Number in Group	Ave. Wgt. in Grams at Start of Expt.	Ave. Wgt. in Grams at Autopsy	Length of Expt.	Ave. Size of Thyroid at Autopsy
Thiouracil	100	196	9 mos.	8.0 x 4.0 mm.
.025 gm. in water				
1 rat	(100)	(196)		8.0 x 4.0 mm.
Thiouracil	127	242	9 mos.	7.5 x 3.0 mm.
.025 gm. by tube				
2 rats	(108)	(278)		8.0 x 3.0 mm.
	(145)	(206)		7.0 x 3.0 mm.
Thiouracil	154	243	9 mos.	6.6 x 3.3 mm.
.05 gm. in water				
3 rats	(188)	(296)		7.0 x 4.0 mm.
	(129)	(208)		6.0 x 3.0 mm.
	(145)	(224)		7.0 x 3.0 mm.
Thiouracil	186	272	9 mos.	8.6 x 4.0 mm.
.05 gm. by tube				
3 rats	(189)	(326)		9.0 x 5.0 mm.
	(200)	(316)		9.0 x 4.0 mm.
	(168)	(174)		8.0 x 3.0 mm.
Average	152	247	9 mos.	7.7 x 3.6 mm.
Control	152	240	9 mos.	4.8 x 2.0 mm.
5 rats	(109)	(282)		5.0 x 2.0 mm.
	(105)	(152)		4.0 x 2.0 mm.
	(157)	(178)		5.0 x 2.0 mm.
	(198)	(306)		5.0 x 2.0 mm.
	(202)	(284)		5.0 x 2.0 mm.

APPENDIX F

Animal Groups and Number in Group	Ave. Wgt. in Grams at Start of Expt.	Ave. Wgt. in Grams at Autopsy	Length of Expt.	Ave. Size of Thyroid at Autopsy
Thiouracil .025 gm. in water 2 rats	110	193	1 yr.	7.0 x 3.0 mm.
	(109)	(210)		8.0 x 3.0 mm.
	(110)	(176)		6.0 x 3.0 mm.
Thiouracil .025 gm. by tube 4 rats	51	262	1 yr.	7.0 x 3.0 mm.
	(53)	(337)		8.0 x 3.0 mm.
	(48)	(201)		6.0 x 3.0 mm.
	(52)	(208)		7.0 x 3.0 mm.
	(49)	(201)		7.0 x 3.0 mm.
Thiouracil .05 gm. in water 3 rats	47	178	1 yr.	8.0 x 3.3 mm.
	(44)	(190)		8.0 x 3.0 mm.
	(48)	(212)		7.0 x 4.0 mm.
	(50)	(203)		9.0 x 3.0 mm.
Thiouracil .05 gm. by tube 4 rats	114	199	1 yr.	7.0 x 4.0 mm.
	(122)	(210)		8.0 x 5.0 mm.
	(113)	(193)		6.0 x 3.0 mm.
	(119)	(202)		7.0 x 5.0 mm.
	(102)	(190)		7.0 x 3.0 mm.
Average	78	210	1 yr.	7.2 x 3.5 mm.
Control 10 rats	81	259	1 yr.	4.5 x 2.0 mm.
	(119)	(230)		5.0 x 2.0 mm.
	(116)	(226)		4.0 x 2.0 mm.
	(110)	(213)		4.0 x 1.5 mm.
	(120)	(222)		4.0 x 2.0 mm.
	(121)	(225)		5.0 x 3.0 mm.
	(38)	(214)		5.0 x 2.0 mm.
	(45)	(239)		6.0 x 2.0 mm.
	(43)	(240)		3.0 x 1.0 mm.
	(40)	(213)		4.0 x 1.5 mm.
	(52)	(363)		5.0 x 3.0 mm.

PLATE 1

EXPLANATION OF FIGURE

Figure 1 Pituitary gland of one month control animal. Section shows the normal size and cellular structure of the cells of the anterior hypophysis X 500.

ABBREVIATIONS

e.-----eosinophile

b.-----basophile

s.-----sinusoid

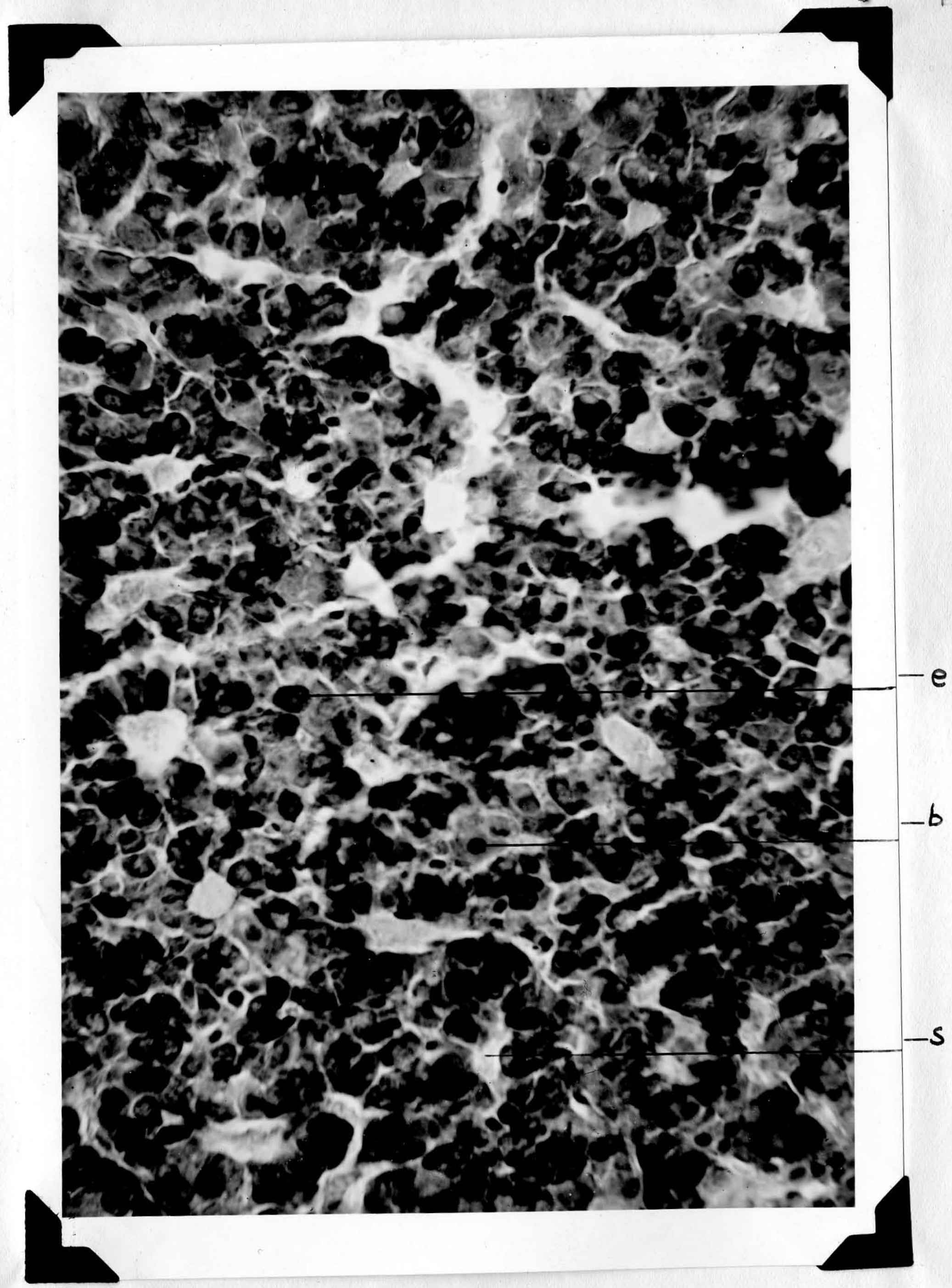

Figure 1

PLATE 2

EXPLANATION OF FIGURE

Figure 2 Pituitary gland of one month experimental animal. Section shows the changes in the size and cell structure of animal fed 0.05 gram of 2-Thiouracil by tube for one month X 500.

ABBREVIATIONS

Same as Figure 1.

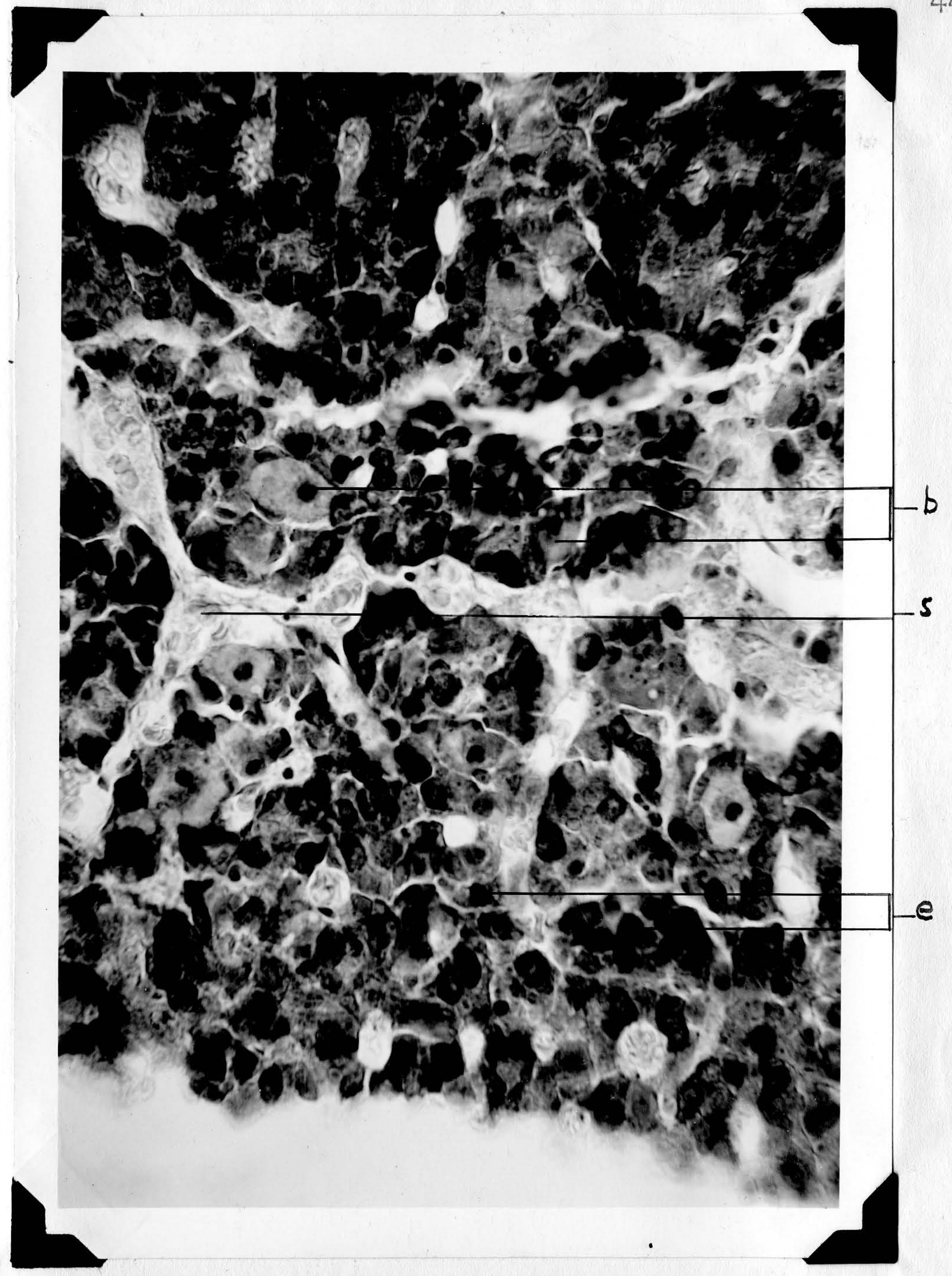

Figure 2

PLATE 3

EXPLANATION OF FIGURE

Figure 3 Thyroid gland of one month control animal. Section shows the normal follicular structure and normal follicular epithelial cells of low height and pycnotic nuclei. Stored colloid is evident in the lumen of the follicle. X 500.

ABBREVIATIONS

c.-----colloid in follicle lumen

p.n.--pycnotic nuclei

c.c.--cuboidal cell of low height

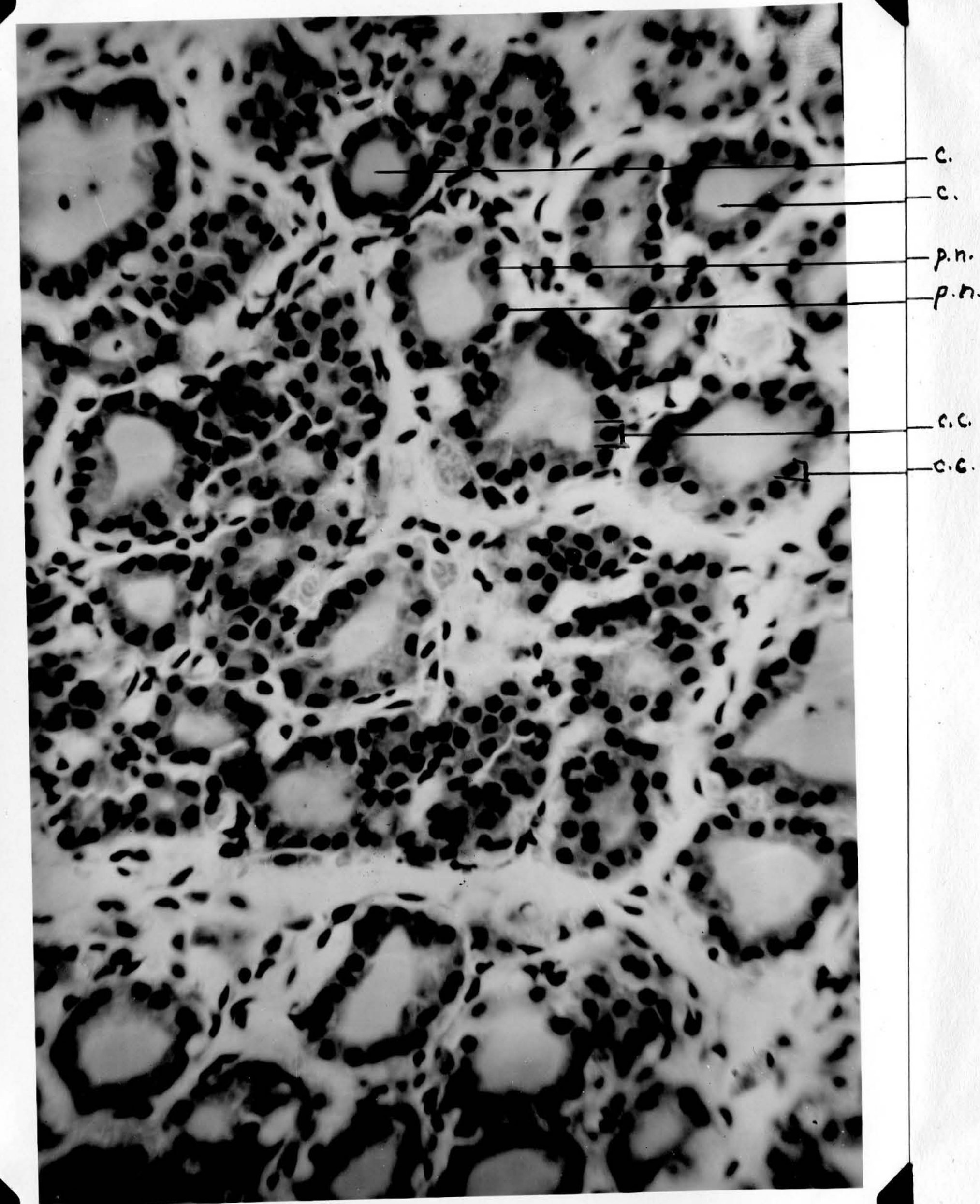

Figure 3

PLATE 4

EXPLANATION OF FIGURE

Figure 4 Thyroid gland of two-month experimental animal fed 0.05 gram of 2-Thiouracil by tube. Section shows the follicles lined by a columnar epithelium. The nuclei are less pycnotic and nucleoli are evident. The colloid in the follicles shows vacuolization due to resorption and is now the active type of colloid. X 500.

ABBREVIATIONS

a.c.--active coloid in follicle lumen

n.----nuclei, less pycnotic, nucleoli present

v.----vacuole of resorption

c.e.--columnar epithelium

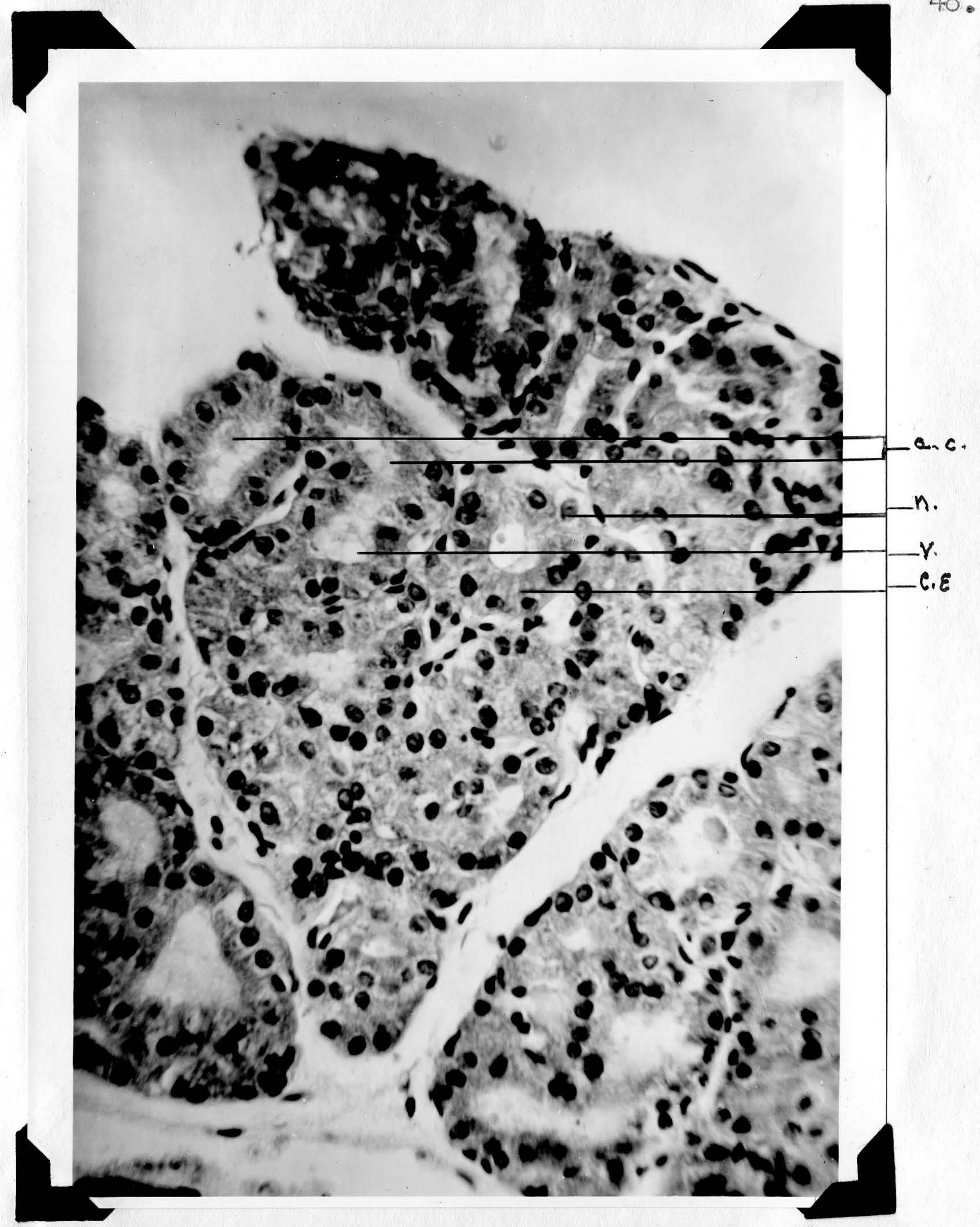

Figure 4

PLATE 5

EXPLANATION OF FIGURE

Figure 5 Thyroid gland of two-month experimental animal fed 0.05 gram of 6-n-propyl thiouracil by tube. Section shows the follicles lined by a columnar epithelium of greater height than seen in Figure 4. Capillary enlargment is apparent. X 500.

ABBREVIATIONS

Same as in Figure 4.

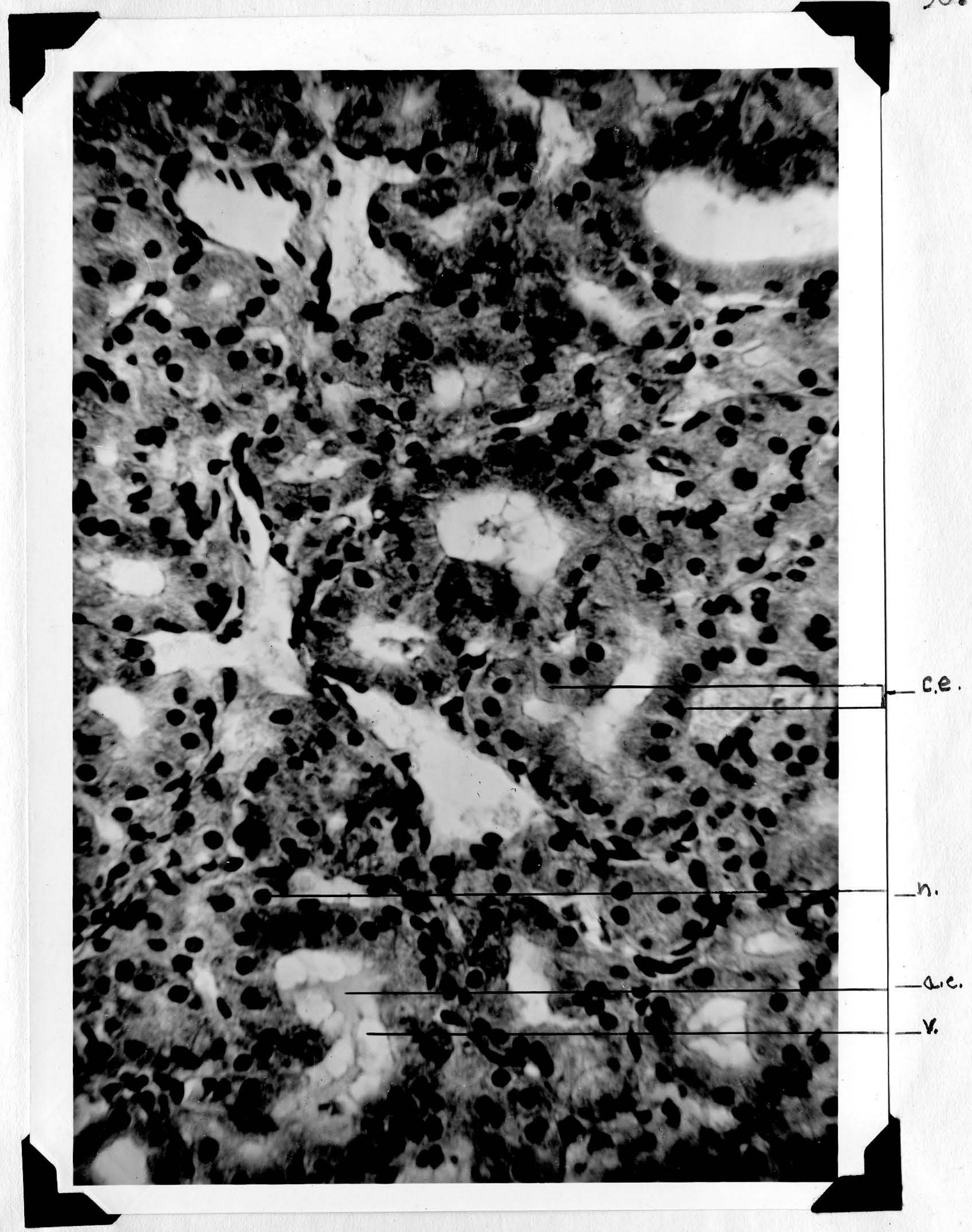

Figure 5

PLATE 6

EXPLANATION OF FIGURE

Figure 6 Thyroid gland of four-month experimental animal fed 2-Thiouracil, 0.05 gram, by tube. Section shows the beginning of the follicle disorganization and the absence of the lumen from the circular masses of follicular epithelial cells. The height of the epithelial cells is not so high as those cells of follicles seen in Figure 4 and yet they are higher than those follicle cells of Figure 3. X 500.

ABBREVIATIONS

Same as in Figure 4.

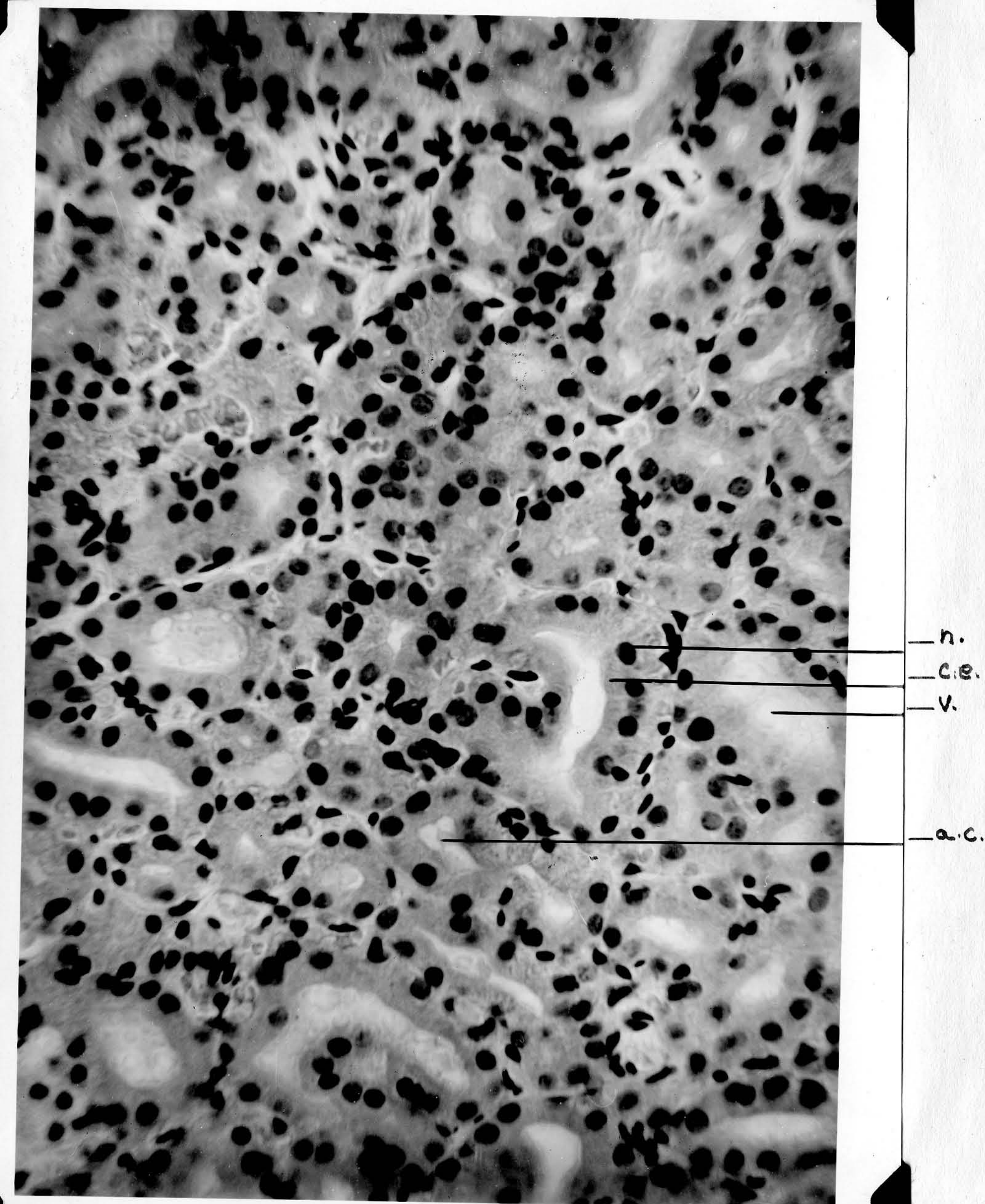

Figure 6

PLATE 7

EXPLANATION OF FIGURE

Figure 7 Thyroid gland of four-month experimental animal fed 0.05 gram of 6-n-propyl thiouracil by tube. Section shows an increased disorganization of the follicles. Many of the follicular lumina are greatly enlarged and in these is a granular substance. Some of the lumina are completely empty of colloid. In this section, the height of the follicular epithelium is still great and has not begun to decrease. X 500.

ABBREVIATIONS

Same as in Figure 4.

g.s.--granular substance

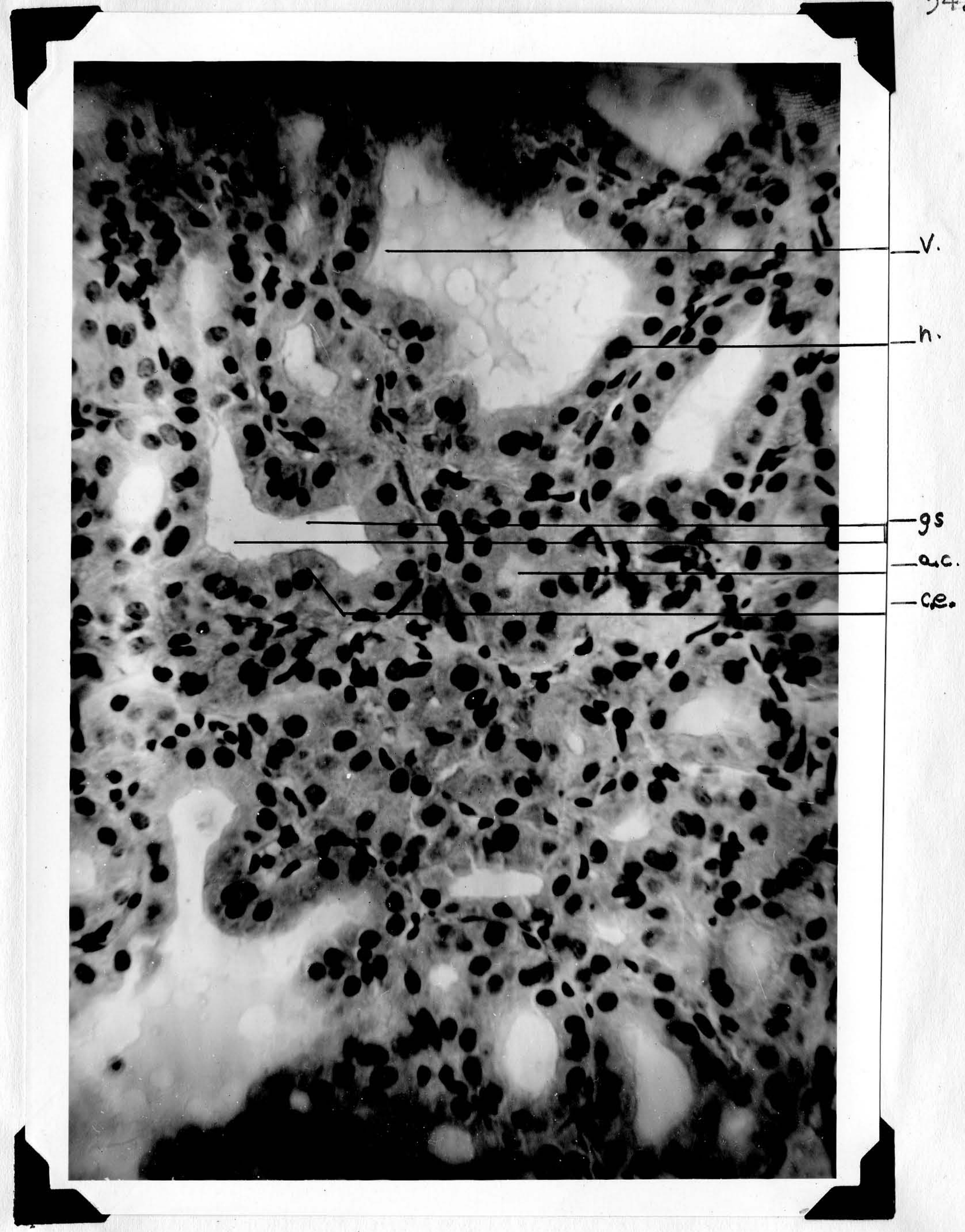

Figure 7

PLATE 8

EXPLANATION OF FIGURE

Figure 8 Thyroid gland of six-month experimental animal fed 0.025 gram of 2-Thiouracil in food. Section shows a development phase similar to that seen in Figure 6. X 500.

ABBREVIATIONS

Same as in Figure 4.

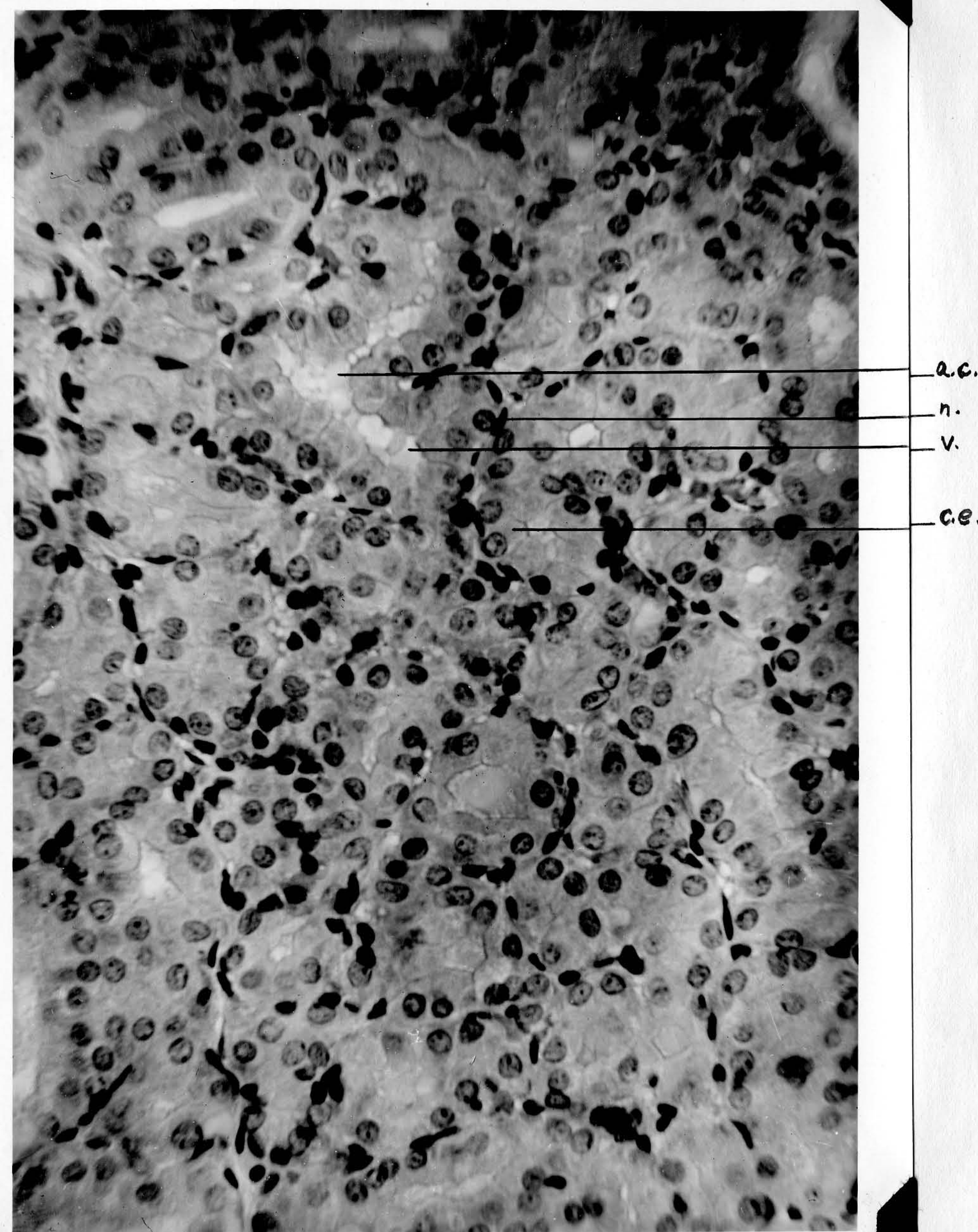

Figure 8

PLATE 9

EXPLANATION OF FIGURE

Figure 9 Thyroid gland of one year experimental animal fed 0.05 gram of 2-Thiouracil in drinking water. Section shows a return to near normalcy with pycnotic nuclei, inactive colloid and, an organized follicular structure. Note the presence of the small follicles and the active colloid indicating the activity of the drug. X 500.

ABBREVIATIONS

v.-----vacuole

a.c.--active colloid

p.n.--pycnotic nuclei

c.c.--cuboidal cell

c.-----colloid

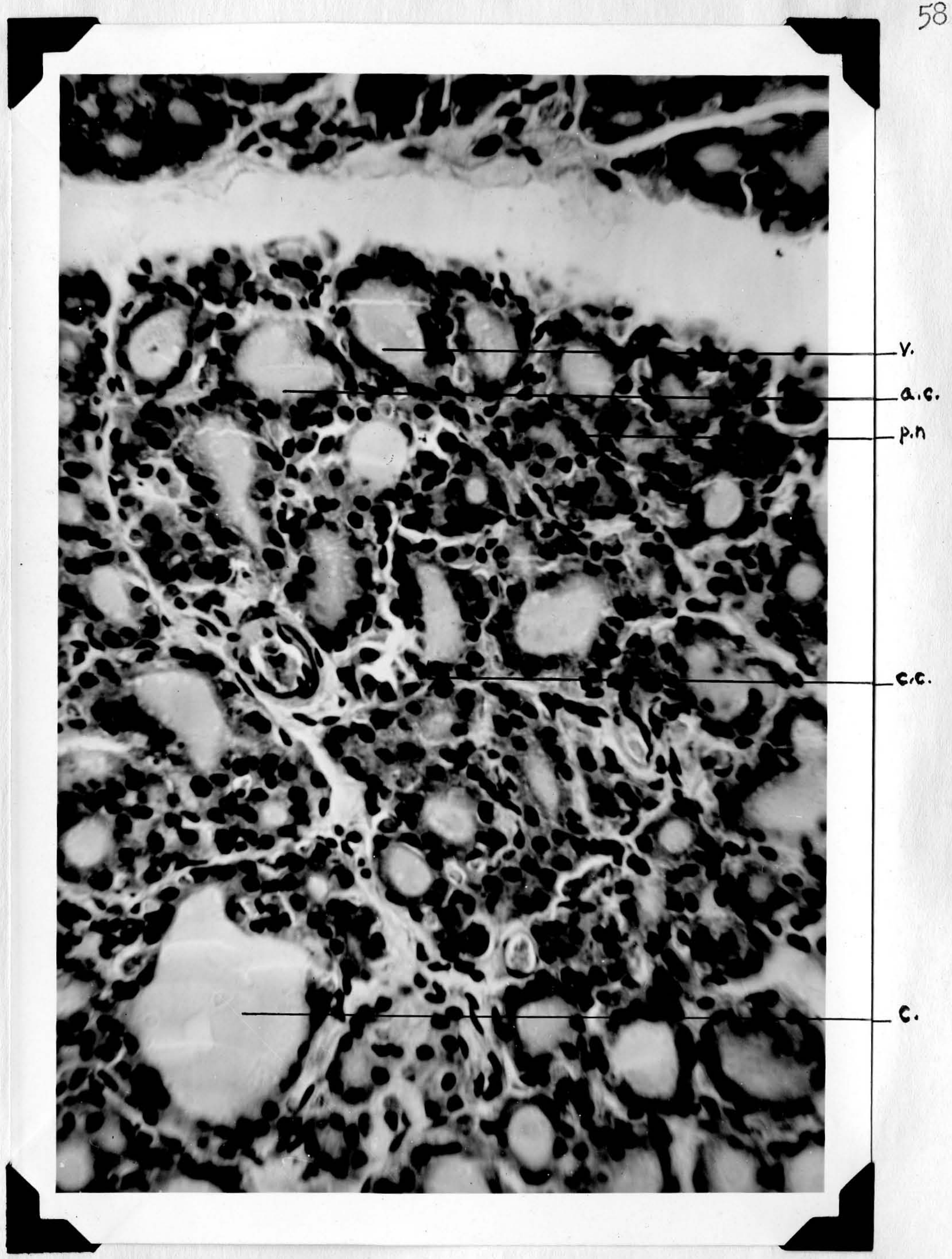

Figure 9

PLATE 10

EXPLANATION OF FIGURE

Figure 10 Thyroid gland of a one year control animal. Section shows many large follicles filled with inactive colloid. There are two follicles which contain active colloid indicating a normal gland activity. The epithelium is cuboidal to almost flat in many of the follicles and indicates a low level of activity in these follicles. X 500.

ABBREVIATIONS

Same as in Figure 9.

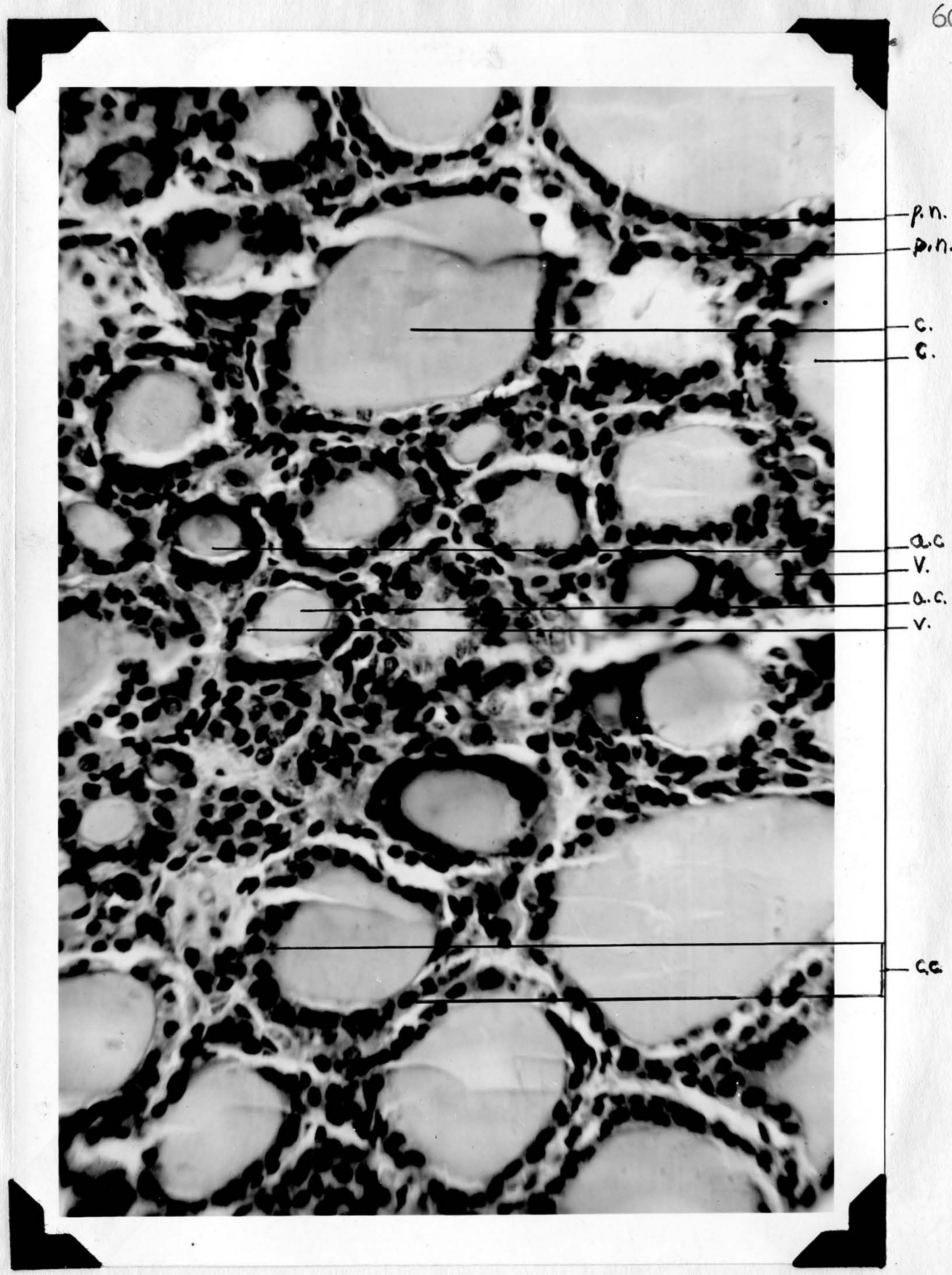

Figure 10

APPROVAL SHEET

The thesis submitted by Gareth Benway Gish has been read and approved by three members of the Department of Anatomy.

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the thesis is now given final approval with reference to content, form, and mechanical accuracy.

The thesis is therefore accepted in partial fulfillment of the requirements for the Degree of Master of Science.

May 29, 1951
Date

Arthur J. Gatz
Signature of Adviser